

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE  
COMPANY, JOHN HANCOCK  
VARIABLE LIFE INSURANCE  
COMPANY and MANULIFE  
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

**ABBOTT'S CORRECTED DEPOSITION DESIGNATIONS AND  
COUNTER DESIGNATIONS FOR LISE LOBERG**

Defendant Abbott Laboratories (“Abbott”) respectfully submits the attached corrected deposition designations and counter-designations for the February 2, 2007 deposition of Lise Loberg, Toxicologist, ABT-518 Team, Abbott Laboratories.

Dated: February 22, 2008

Respectfully submitted,

ABBOTT LABORATORIES

By: /s/ Eric J. Lorenzini  
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*Counsel for Abbott Laboratories*

**CERTIFICATE OF SERVICE**

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 22, 2008.

Date: February 22, 2008.

\_\_\_\_\_  
/s/ Ozge Guzelsu

### **Lise Loberg Deposition Designations**

<b>Depo Date</b>	<b>Witness</b>	<b>Hancock Designation</b>	<b>Abbott Counter Designation</b>	<b>Abbott Designation</b>	<b>Deposition Exhibit</b>	<b>Plaintiff Exhibit</b>	<b>Defendant Exhibit</b>
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2/2/2007	Loberg, Lise			9:14-10:22			
2/2/2007	Loberg, Lise			12:2-12:19			
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<b>Depo Date</b>	<b>Witness</b>	<b>Hancock Designation</b>	<b>Abbott Counter Designation</b>	<b>Abbott Designation</b>	<b>Deposition Exhibit</b>	<b>Plaintiff Exhibit</b>	<b>Defendant Exhibit</b>
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## **Color Key to Deposition Designations**

**Designation by Plaintiffs**

**Counter Designation by Defendants**

**Designation by Defendants**

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1 UNITED STATES DISTRICT COURT

2 FOR THE

3 DISTRICT OF MASSACHUSETTS

4

5 JOHN HANCOCK LIFE INSURANCE )

6 COMPANY, JOHN HANCOCK )

7 VARIABLE LIFE INSURANCE )

8 COMPANY, and MANULIFE )

9 INSURANCE COMPANY (f/k/a )

10 INVESTORS PARTNER INSURANCE ) Civil Action No.

11 COMPANY), ) 05-11150-DPW

12 Plaintiffs, )

13 -vs- )

14 ABBOTT LABORATORIES, )

15 Defendant. )

16

17 The videotaped deposition of LISE

18 LOBERG, called for examination, taken pursuant to

19 the Federal Rules of Civil Procedure of the United

20 States District Courts pertaining to the taking of

21 depositions, taken before THERESA A. VORKAPIC, a

22 Notary Public within and for the County of Kane,

23 State of Illinois, and a Certified Shorthand

24 Reporter, CSR No. 84-2589, of said state, at Suite

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1 1300, Two North LaSalle Street, Chicago, Illinois,  
2 on the 2nd day of February, A.D. 2007, at  
3 approximately 9:27 a.m.

4 PRESENT:

5 CHOATE HALL & STEWART, LLP,

6 (Two International Place,

7 Boston, Massachusetts 02110,

8 617-248-5000), by:

9 MR. JOSEPH M. ZWICKER,

10 jzwicker@choate.com,

11 appeared on behalf of Plaintiffs;

12 MUNGER TOLLES & OLSON, LLP,

13 (355 South Grand Avenue, 35th Floor,

14 Los Angeles, California 90071-1560,

15 213-683-9207), by:

16 MR. ERIC J. LORENZINI,

17 eric.lorenzini@mto.com,

18 appeared on behalf of Defendant.

19

20 VIDEOTAPED BY: SCOTT CAMPBELL, Legal

21 Videographer, Esquire Deposition

22 Services

23 REPORTED BY: THERESA A. VORKAPIC,

24 C.S.R. Certificate No. 84-2589

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1 Q. Good morning, Dr. Loberg.

2 A. Hi.

3 Q. I represent John Hancock and other

4 Plaintiffs and I'm going to be asking you some

5 questions this morning, okay. If I ask you a

6 question that you don't understand, ask me for

7 clarification and I'll try to clarify it, okay.

8 The other rule is you have to answer

9 questions verbally, not with nods of the head.

10 Got it?

11 A. Yes.

12 Q. The Reporter can't pick up a head nod.

13 If you need a break, ask and we'll give you one,

14 okay?

15 A. Okay.

16 Q. Where are you presently employed?

17 A. Abbott Laboratories.

18 Q. What's your job?

19 A. I'm a toxicologist.

20 Q. Is that your official title,

21 toxicologist?

22 A. Yes. Research scientist, toxicologist.

23 Q. What is toxicology?

24 A. It's the -- the simplest explanation is

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1 the study of poisons on the body and what that

2 means is we study the safety of drugs.

3 Q. How long have you been a toxicologist

4 at Abbott?

5 A. At Abbott, seven years.

6 Q. Since 2000?

7 A. Yeah, December 1999.

8 Q. Have your responsibilities changed

9 between December 1999 and today?

10 A. Yes. I have had two promotions. My  
11 responsibilities have not changed dramatically. I  
12 do pretty much the same work that I did before.

13 Q. Tell us what your responsibilities at  
14 Abbott are as toxicologist.

15 A. As a study director, I run studies  
16 which means that I set up the study design, make  
17 sure that the study is conducted according to the  
18 appropriate regulations, analyze the results and  
19 write the report.

20 I have other duties as a toxicology  
21 representative on project teams, and in that case,  
22 what I do is present results from toxicology  
23 studies at project meetings.

24 Q. What was your job before Abbott?

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1 A. Prior to Abbott, I worked at IIT

2 Research Institute for four years.

3 Q. Doing what?

4 A. Conducting research, molecular

5 toxicology research.

6 Q. Before IIT?

7 A. Before that I was in graduate school at

8 the University of Cincinnati.

9 Q. What degree did you earn and when?

10 A. I earned a Ph.D. in toxicology in 1996.

11 Q. What was your undergraduate education?

12 A. My undergraduate education was at John

13 Carroll University. I have a Bachelor of Science

14 degree in psychology.

15 Q. What year?

16 A. 1989.

17 Q. How did you prepare for your deposition

18 today?

19 A. I met with Eric.

20 Q. When?

21 A. Tuesday.

22 Q. For how long?

23 A. A couple of hours.

24 Q. Who was present?

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1 A. It was myself and Eric and Pete Witte

2 was there for part of the time.

3 Q. You understood he was a lawyer for

4 Abbott?

5 A. Yes.

6 Q. The meeting took place at Abbott Park?

7 A. Yes.

8 Q. Is that where you work?

9 A. Yes.

10 Q. That's where you've worked since 2000?

11 A. Yes. I was at Abbott's facility in

12 Germany for a year and a half.

13 Q. What year was that?

14 A. That was starting 2002 through August

15 2003.

16 Q. So for the period 2000, 2001 you were

17 in at Abbott Park in Illinois, right?

18 A. That's correct.

19 Q. There came a time when you became

20 assigned to the project team for a compound then

21 under development then known as ABT-518, correct?

22 A. Correct.

23 Q. What was your role in connection with

24 the development of ABT-518?

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1 A. I believe I ran a couple of the studies  
2 on that project, not all of them, and I acted as a  
3 representative to the project team. I presented  
4 results.

5 Q. What year were you assigned to the  
6 development of ABT-518?

7 A. 2000 I think. I don't know.

8 Q. Who is Bill Bracken?

9 A. At that time Bill Bracken was the  
10 manager of toxicology. I reported to him.

11 Q. Did there come a time when you took  
12 over his responsibilities?

13 A. Not entirely.

14 Q. You said you ran two studies in  
15 connection with 518; is that right?

16 A. I don't know how many. I think maybe  
17 one or two. I don't recall exactly.

18 Q. What did you do -- sorry I cut you off.  
19 Finish your answer.

20 A. I don't remember exactly who was the  
21 study director on the studies.

22 Q. The study director for toxicology?

23 A. Yes. So in a development program there  
24 are several different studies that are conducted.

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1 Q. When you say studies, you mean

2 toxicology studies, right?

3 A. Correct. I mean toxicology studies.

4 And each one most likely has a different study

5 director. As a representative, I'm not

6 necessarily the study director on all the studies

7 involved.

8 Q. Were you the study director for either

9 of the two, one or toxicology studies that you've

10 discussed?

11 A. I would have to see a listing of all

12 the studies with the study directors to know for

13 sure.

14 Q. In any event, with respect to the one

15 or two studies that you testified to, you

16 testified that you ran those studies; is that

17 right? Let me ask you a different question.

18 What did you do with respect to the one

19 or two studies that you were involved with 518?

20 A. I presented results from those studies

21 at project team meetings.

22 Q. Where did you get the results that you

23 presented?

24 A. From internal meetings at which results

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1 were presented from the people who obtained those  
2 results.

3 Q. These were other people involved in the  
4 toxicology component of the development?

5 A. Correct, yes.

6 Q. What people were those?

7 A. In any given toxicology study, there is  
8 the study director, there is the pathologist, and  
9 then for additional assays there may be other  
10 scientists, for example, drug analysis.

11 Q. Assays are tests?

12 A. Yeah. Assays and tests are the same  
13 thing.

14 Q. So is it fair to say that you reported  
15 the results of information provided to you by  
16 others in connection with your toxicology work on  
17 518?

18 A. Yes, that's correct.

19 Q. Who did you report to during the time  
20 you were involved on 518?

21 A. I reported to Bill Bracken who was the  
22 manager of toxicology.

23 Q. In connection with your work on  
24 ABT-518, did you draft monthly highlight reports?

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1 BY MR. ZWICKER:

2 Q. Are you familiar with the MMPI Working

3 Group?

4 A. Yes.

5 Q. What is it?

6 A. For every compound that we have in

7 development, there's a project team that is

8 comprised of a number of individuals from the

9 different functional areas that contribute to

10 development.

11 Q. Were you a member of the MMPI working

12 team for 518?

13 A. I can't say that I was a standing

14 member of the group. I know that I attended a few

15 meetings and presented results. I don't believe

16 that I would have attend all of the meetings.

17 Q. Why not?

18 A. I was at too junior of a position at

19 the time.

20 Q. Were you working on toxicology issues

21 for other compounds at the same time you were

22 working on 518?

23 A. Yes.

24 Q. How many?

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1 compound on chromosomes, whether there is damage  
2 to the chromosomes.

3 Q. What's cytotoxicity?

4 A. Cytotoxicity is the effect on whole  
5 cells so if a compound kills cells invitro.

6 Q. What's ligand binding assays?

7 A. Ligand binding assays I'm less familiar  
8 with. I don't know what that refers to.

9 Q. Am I right that you were not involved  
10 as the study director in connection with any  
11 studies of genotoxicity, clastogenicity,  
12 cytotoxicity and ligand binding assays?

13 A. I would not have been the study  
14 director on any of those studies. That's not my  
15 expertise.

16 Q. So there was toxicity work that took  
17 place with respect to 518 before you became  
18 involved; is that fair? Let me strike that.

19 There was toxicity work done for 518  
20 that you weren't involved in, correct?

21 A. Correct.

22 MR. ZWICKER: 2.

23 (WHEREUPON, a certain document  
24 was marked Loberg Deposition

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1 specifically, but it looks like it.

2 Q. Your name is there, right?

3 A. Yes.

4 Q. Were you aware that notes were taken at

5 MMPI Working Group meetings?

6 A. Yes.

7 Q. Who took the notes?

8 A. I don't remember.

9 Q. Was it Diane D'Amico?

10 A. It may have been. I don't remember.

11 Q. Do you know what happened to the notes

12 that the person took?

13 A. No.

14 Q. So you never saw draft written minutes

15 for these meetings; is that right?

16 A. Not that I recall.

17 Q. You might have?

18 A. I might have.

19 Q. Read the toxicology portion of Exhibit

20 No. 3 and let me know if it refreshes your

21 recollection of a meeting that took place in

22 January 2001 regarding 518?

23 A. I remember --

24 Q. Let me ask you a question.

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1 A. Yes.

2 Q. The meeting minutes refer to two  
3 toxicity studies, correct?

4 A. Yes.

5 Q. Do you remember in January of 2001 you  
6 were involved in two toxicity studies in  
7 connection with 518?

8 A. Yes. I remember this six-week study  
9 and a three-month study. I wouldn't be able to  
10 say it was January 2001, but I do remember the  
11 studies.

12 Q. You were the study director for those  
13 two studies?

14 A. I believe I was the study director for  
15 the six-week study, and I don't remember who the  
16 study director was for the three-month study.

17 Q. Who else could it have been?

18 A. It could have been any one of my  
19 toxicology colleagues at the time.

20 Q. If you weren't the study director, you  
21 were the presenter with respect to the three-month  
22 study; is that correct?

23 A. Yes.

24 Q. Was it your understanding in the period

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1 of January 2001 that there were two ongoing  
2 toxicology studies for 518, the three-month study  
3 and the six-week study; is that your recollection?

4 A. Based on these minutes, yes, in  
5 January.

6 Q. You have a recollection there were two  
7 ongoing studies taking place for 518, a six week  
8 and a three month?

9 A. Right, but the exact timing --

10 Q. Fair enough. Let's start with the  
11 six-week study. The minutes say the main purpose  
12 of the six-week study is to determine an etiology  
13 and mechanism for the steatosis noted in previous  
14 toxicity studies."

15 Do you see that?

16 A. Yes.

17 Q. Can you explain that in plain English,  
18 the objective of the six-week study?

19 A. Yeah. Steatosis is a finding in the  
20 liver that was seen in a study done earlier and we  
21 designed this six-week study in order to find out  
22 more about what that steatosis was, what was  
23 discussing causing it and what the specific  
24 biochemical mechanism might be.

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1 Q. You said a finding in the liver.

2 What finding in the liver?

3 A. Steatosis.

4 Q. What is steatosis?

5 A. It's a buildup of fatty material in the  
6 liver.

7 Q. And the purpose of the study was to  
8 determine whether there was a relationship between  
9 518 and steatosis?

10 MR. LORENZINI: Objection.

11 BY THE WITNESS:

12 A. The purpose of the study was to  
13 recreate the steatosis and look at some of the  
14 earlier time points before the steatosis became  
15 I'll say visible, but that's visible upon  
16 microscopic analysis of the liver tissue.

17 So the purpose was to look at earlier  
18 time points and look at a number of different  
19 tests we could do in cells or in tissue from the  
20 liver looking at some of the things that we know  
21 to be related to steatosis.

22 BY MR. ZWICKER:

23 Q. Was your objective to see if there was  
24 a correlation between 518 and steatosis in the

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1 liver?

2 A. That would have been an objective, yes.

3 Q. The minutes also refer to three-month  
4 study.

5 Do you see that?

6 A. Uh-huh.

7 Q. What was the purpose of the three-month  
8 study?

9 A. The three-month GLP study was one that  
10 was conducted in order to support clinical trials  
11 of a certain duration.

12 Q. What's GLP mean?

13 A. GLP is good laboratory practices. It's  
14 is a FDA regulation that we adhere to.

15 Q. How would the three-month GLP study  
16 support Phase I clinical trials?

17 A. It's required to have preclinical  
18 studies in two species of the same or longer  
19 duration than the clinical trials planned and  
20 during the course of development, successively  
21 longer toxicology studies are conducted in order  
22 to support successively longer clinical trials.

23 Q. So the objective would be to determine  
24 tolerability in animals as a precursor to starting

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1 Phase I trials?

2 MR. LORENZINI: Objection.

3 BY THE WITNESS:

4 A. Yes. The purpose of these studies is  
5 to determine safety margins so one of the  
6 objectives of the studies is to identify  
7 toxicology or toxicity and to then look at what  
8 was the dose and the exposure at that level of  
9 toxicity compared to the dose and the exposure at  
10 the level of efficacy where the drugs are  
11 effective.

12 Q. In your mind, was the three-month study  
13 important to a successful Phase I clinical trial?

14 MR. LORENZINI: Objection.

15 BY THE WITNESS:

16 A. I think that the three-month study was  
17 conducted to support beyond Phase I. I think that  
18 -- I don't recall this specific program, but in  
19 general we have a shorter study, a one-month study  
20 that's GLP that's supporting the Phase I clinical  
21 trial. And the three-month study is then  
22 conducted at the time the Phase I clinical trial  
23 is ongoing or afterwards in order to support Phase  
24 II. That's the typical development scenario.

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1 Q. I'm talking about a period in March of  
2 2001.

3 Did you learn in March of 2001 that all  
4 development activity for 518 had been put on hold?

5 A. No.

6 Q. In March of 2001, did you learn that  
7 development activity for toxicology had been put  
8 on hold?

9 A. No. I don't remember that in March.

10 Q. Do you remember attending any meetings  
11 with Dr. Nabulsi in which he told you that  
12 Dr. Leiden had directed that the 518 project be  
13 terminated?

14 A. No.

15 Q. Did you meet with Dr. Nabulsi?

16 A. I don't think that I ever met with him  
17 one on one. He may have been at some of the  
18 meetings I was at.

19 Q. Do you recall hearing from any other  
20 members of the 518 project team that development  
21 activities for 518 had been terminated as of March  
22 2001?

23 A. I don't remember that.

24 (WHEREUPON, a certain document

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1 was marked Loberg Deposition  
2 Exhibit No. 7, for identification,  
3 as of 2/2/07.)  
4 (WHEREUPON, the document was  
5 tendered to the witness.)

6 BY MR. ZWICKER:

7 Q. Before the witness is Loberg Exhibit  
8 No. 7, which is an oncology status report from  
9 March 16, 2001.

10 Dr. Loberg, if you could read Section 4  
11 entitled Toxicology and let me know when you're  
12 done.

13 A. Okay.

14 Q. In the middle of the paragraph, it  
15 says: "The group plans to complete only those  
16 analyses already started. They will not initiate  
17 any new analyses; however, they may decide to go  
18 back and look at the long chain fatty acids."

19 Do you see that?

20 A. Yes.

21 Q. Did you learn on around March 16, 2001  
22 that only toxicology work under way would be  
23 completed?

24 A. No, I don't recall that.

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1 Q. Do you recall in March of 2001 that  
2 there was any restriction upon completing the two  
3 toxicology studies we've discussed, the six-week  
4 study and the three-month study?

5 A. No. I don't remember any restrictions.

6 Q. Did you write Section 4 of this  
7 document?

8 A. I didn't write this section, no.

9 Q. But you remember you were a member of  
10 the toxicology team, weren't you?

11 A. Yes.

12 Q. Wouldn't you have expected that you  
13 would have learned that there had been a hold on  
14 toxicology activities as a member of the team?

15 MR. LORENZINI: Objection. Assumes facts not  
16 in evidence.

17 BY THE WITNESS:

18 A. If there had been a hold, I would have  
19 been aware of it.

20 BY MR. ZWICKER:

21 Q. Are you saying you don't remember one  
22 way or another whether there was a hold on some  
23 toxicology activities? Is that your testimony?

24 MR. LORENZINI: Objection.

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1 BY THE WITNESS:

2 A. I don't recall that there was a hold on  
3 any activities at that time.

4 BY MR. ZWICKER:

5 Q. The sentence that says they will not  
6 initiate any new analyses, however, they may  
7 decide to go back and look at long chain fatty  
8 acids, do you see that?

9 A. Yes.

10 Q. You have no reason to think that that  
11 sentence is incorrect, do you?

12 A. No, I don't. I don't think this refers  
13 to any particular hold on the study, either. What  
14 this refers to is in that six-week study, there  
15 was a long list of various tests that we could  
16 have done, and we conducted a number of those and  
17 earlier in this paragraph it says the data was  
18 available and analyzed and there were no glaring  
19 effects on mitochondrial function.

20 So what this means to me is that by  
21 completing those analysis started and not  
22 initiating any new analyses is that we had learned  
23 pretty much what we needed to learn from the  
24 analysis that had already been completed and that

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1 peroxisomal function whereas the other analyses  
2 looked more specifically at mitochondrial  
3 function.

4 Q. What's peroxisomal function?

5 A. The mitochondrial and peroxisomes are  
6 subcellular functions that both have different  
7 functions in terms of lipid metabolism or storage  
8 maybe, and what we were looking at is how that  
9 lipid metabolism is affected in the liver so we  
10 were looking at mitochondria and then the long  
11 chain fatty acids was to look at peroxisomes.

12 Q. Did you view the long chain fatty acid  
13 analysis as an important analysis?

14 MR. LORENZINI: Objection.

15 BY THE WITNESS:

16 A. I viewed it as an analysis that would  
17 add to what we had already had with the  
18 mitochondria, but it didn't necessarily -- I don't  
19 know that it was particularly crucial. It was  
20 just another piece of evidence.

21 BY MR. ZWICKER:

22 Q. Do you recall that Abbott put a hold on  
23 performing the long chain fatty acid analysis?

24 A. I don't recall a hold on that.

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1 Q. Isn't it true that the necropsy  
2 analysis for the three-month study had been put on  
3 hold by Abbott as of April 2001?

4 A. The necropsy itself really can't be put  
5 on hold.

6 Q. My question is the analysis.

7 A. So the histopathology analysis?

8 Q. Is histopathology and necropsy the  
9 same?

10 A. Not -- technically, no, they're not the  
11 same.

12 Q. But the necropsy analysis is the  
13 histopathology, that's your point?

14 MR. LORENZINI: Objection. Misstates the  
15 witness's testimony.

16 BY MR. ZWICKER:

17 Q. Necropsy is the collection of the  
18 tissues?

19 A. Right.

20 Q. Histopathology is the analysis of the  
21 tissues, right?

22 A. Yes, yeah.

23 Q. Was it your understanding that the  
24 analysis of the issues for the three-month study

Loberg, Lise (Linked) 02/02/2007 9:27:00 AM

1 had been put on hold by April of 2001?

2 MR. LORENZINI: Objection.

3 BY THE WITNESS:

4 A. I vaguely recall that there was a hold

5 on the histopathology on the three-month study. I

6 don't know exactly when that occurred.

7 MR. ZWICKER: Eight.

8 (WHEREUPON, a certain document

9 was marked Loberg Deposition

10 Exhibit No. 8, for identification,

11 as of 2/2/07.)

12 (WHEREUPON, the document was

13 tendered to the witness.)

14 BY MR. ZWICKER:

15 Q. Before the witness is Loberg Exhibit

16 No. 8 which are MMPI Working Group minutes from

17 April 12, 2001.

18 Dr. Loberg, would you review the

19 section relating to toxicology?

20 A. Okay.

21 Q. You were the presenter with respect to

22 the six-week and three-month studies on April 12,

23 2001, weren't you?

24 A. That's correct.

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1 Q. Were you also the medical director --

2 the study director for both studies at this point?

3 Can you recall?

4 A. I was the study director on the

5 six-week study. I don't think I was the study

6 director on the three-month study.

7 Q. Does looking at this document refresh

8 your recollection about who was?

9 A. No, it doesn't.

10 Q. Does reviewing this document refresh

11 your recollection that necropsy analysis of

12 samples from the three-month study was put on hold

13 by April 12, 2001?

14 MR. LORENZINI: Objection. Vague and

15 ambiguous.

16 BY THE WITNESS:

17 A. I remember that the -- again, this is

18 using the wrong terminology, but the

19 histopathology was put on hold.

20 BY MR. ZWICKER:

21 Q. Okay. When was the histopathology put

22 on hold?

23 A. I only remember that it was at a point

24 after the necropsy itself would have taken place.

Loberg, Lise (Linked) 02/02/2007 9:27:00 AM

1 I don't remember exactly the date or even the  
2 month that we were asked to put that on hold.

3 Q. It was sometime prior to April 12,  
4 though, it wasn't?

5 MR. LORENZINI: Objection. Mischaracterizes  
6 the testimony.

7 BY THE WITNESS:

8 A. Yeah, it would seem that that's the  
9 case.

10 BY MR. ZWICKER:

11 Q. You've testified that the  
12 histopathology was a significant part of the  
13 study, correct?

14 A. Yes.

15 Q. Why was it put on hold?

16 A. Histopathology is one aspect of the  
17 study that can be placed on hold since the tissues  
18 are held in a fixative and they don't degrade in  
19 that fixative. That is one of the few portions of  
20 a study that can actually be postponed to a later  
21 date.

22 Q. Okay. My question to you is not  
23 whether it could have been put on hold but why it  
24 was it put on hold?

1 A. That I don't really recall -- I don't  
2 recall why it was.

3 Q. Who put it on hold?

4 MR. LORENZINI: Objection.

5 BY THE WITNESS:

6 A. We would have been asked by the project  
7 team or the working group or somebody in the team.

8 BY MR. ZWICKER:

9 Q. Based on your practice and experience,  
10 who would have told you to put the histopathology  
11 portion of the three-month study on hold?

12 MR. LORENZINI: Objection.

13 BY THE WITNESS:

14 A. Based on what I've seen in the seven  
15 years I've worked at Abbott, it's generally a  
16 decision that's made at the team level or at the  
17 level of the leader of the project team or in this  
18 case the Working Group. I'm not sure who  
19 specifically would make a decision like that.

20 BY MR. ZWICKER:

21 Q. Did you have an understanding as of  
22 April 12, 2001 that any other aspects of the  
23 three-month study were also put on hold?

24 A. No.

Loberg, Lise (Linked) 02/02/2007 9:27:00 AM

1 compound. I don't think there were any  
2 significant issues there.

3 BY MR. ZWICKER:

4 Q. Did anyone tell you -- I am sorry if  
5 you weren't finished with your answer. Go ahead.

6 A. And not knowing what the overall  
7 priorities are with different compounds, I didn't  
8 know.

9 Q. Did you know that as of March 16, 2001  
10 that with the exception of the clinical trial that  
11 all development activities with regard to 518 were  
12 put on hold by Dr. Leiden?

13 MR. LORENZINI: Objection. Asked and  
14 answered.

15 BY THE WITNESS:

16 A. In March, no.

17 BY MR. ZWICKER:

18 Q. Were you aware as of April 12, 2001  
19 that any aspects of the development of 518 were  
20 also put on hold?

21 MR. LORENZINI: Objection.

22 BY THE WITNESS:

23 A. At the time of the three-month study  
24 histopathology analysis was put on hold, there may

Loberg, Lise (Linked) 02/02/2007 9:27:00 AM

1 funding status, no.

2 MR. ZWICKER: Theresa, let's mark this as the  
3 next exhibit.

4 (WHEREUPON, a certain document

5 was marked Loberg Deposition

6 Exhibit No. 9, for identification,

7 as of 2/2/07.)

8 (WHEREUPON, the document was

9 tendered to the witness.)

10 BY MR. ZWICKER:

11 Q. Before the witness is Loberg Exhibit  
12 No. 9, MMPI monthly meeting agenda for that April  
13 12, 2001 MMPI Working Group.

14 Dr. Loberg, do you recognize the  
15 handwriting on this document?

16 A. No, I don't.

17 Q. Do you know Diane D'Amico?

18 A. I know of her.

19 Q. Do you recall working with her on 518?

20 A. Remember that she was at some of the  
21 meetings.

22 Q. Look at Roman Numeral I, Toxicology,  
23 L. Loberg; do you see that?

24 A. Uh-huh, yes.

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1 this document it looks like it, yes.

2 Q. Does reading that handwritten note

3 refresh your recollection that Perry Nissen

4 directed that no analysis of the three-month

5 samples be undertaken until further instruction?

6 MR. LORENZINI: Objection.

7 BY THE WITNESS:

8 A. I don't recall specifically that it was

9 Perry Nissen that requested that that not be done.

10 BY MR. ZWICKER:

11 Q. Who do you recall -- sorry. Were you

12 done with your answer?

13 A. I don't recall who.

14 Q. Do you recall somebody directing that

15 the three-month sample -- that analysis of the

16 three-month sample not be completed until further

17 instruction?

18 A. I don't recall exactly when anybody was

19 instructed not to complete that. I just remember

20 that in that study there was a period of time that

21 we waited, but I don't recall exactly when that

22 was -- when that was told to us or requested of

23 us.

24 Q. Having reviewed this document, do you

Loberg, Lise (Linked) 02/02/2007 9:27:00 AM

1 have any doubt that as of April 12, Abbott had put  
2 a hold on analyzing the histopathology results  
3 from the three-month study?

4 MR. LORENZINI: Objection. Vague and  
5 ambiguous. By as of are you including the date  
6 itself, April 12?

7 BY MR. ZWICKER:

8 Q. I'll stand on the question. Can you  
9 answer?

10 A. That prior to this meeting there had  
11 been a hold.

12 Q. As of the date of this meeting?

13 MR. LORENZINI: Objection. Vague and  
14 ambiguous.

15 Could the Court Reporter read the  
16 question back, please?

17 (WHEREUPON, the record was  
18 read by the reporter.)

19 MR. LORENZINI: Objection, but you can  
20 answer.

21 BY THE WITNESS:

22 A. I can't say from reviewing this  
23 document if this was a decision made at this  
24 meeting or prior to this meeting. It may have

Loberg, Lise (Linked) 02/02/2007 9:27:00 AM

1 been made at this meeting.

2 BY MR. ZWICKER:

3 Q. Okay. Let me put the question to you a

4 different way.

5 The document is dated April 12, right?

6 A. Yes.

7 Q. Any doubt in your mind that by the

8 close of business on April 12, 2001 that Abbott

9 had put a hold on processing the histopathology

10 results from the three-month trial?

11 MR. LORENZINI: Objection.

12 BY THE WITNESS:

13 A. That would seem to be the case.

14 BY MR. ZWICKER:

15 Q. Do you know why Abbott put that hold on

16 analyzing those results?

17 MR. LORENZINI: Objection. Lacks foundation.

18 Asked and answered.

19 BY THE WITNESS:

20 A. No. I don't know why.

21 BY MR. ZWICKER:

22 Q. Look at the lower lefthand part of the

23 first page of Exhibit 9. There's more handwritten

24 notes. It says: "Per Perry, kill scenario,

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1 A. Uh-huh. I see that.

2 Q. Do you have any recollection of being  
3 in a meeting where Jeff, Dr. Leiden's views,  
4 regarding the future of 518 were discussed?

5 A. No, I don't.

6 Q. Do you recall there being post meeting  
7 gatherings after Working Group meetings?

8 A. No.

9 Q. Do you ever recall anyone saying Jeff  
10 wants to kill this?

11 A. I don't recall that.

12 Q. Do you know what a white paper is?

13 MR. LORENZINI: Objection. Vague.

14 BY THE WITNESS:

15 A. Yes, I've never written one, but I know  
16 the general concept of what a white paper is.

17 BY MR. ZWICKER:

18 Q. What is it?

19 A. A position statement on an issue.

20 Q. Do you know whether a white paper was  
21 ever written regarding 518?

22 MR. LORENZINI: Objection. Lacks foundation.

23 Vague and ambiguous.

24 (WHEREUPON, a certain document

Loberg, Lise (Linked) 02/02/2007 9:27:00 AM

1 was marked Loberg Deposition

2 Exhibit No. 10, for identification,

3 as of 2/2/07.)

4 (WHEREUPON, the document was

5 tendered to the witness.)

6 BY MR. ZWICKER:

7 Q. Before the witness is Loberg Exhibit

8 No. 10, which is an oncology status report of May

9 11, 2001.

10 Dr. Loberg, would you read Section 4,

11 Toxicology and let me know when you're done?

12 A. Okay.

13 Q. Just focusing your attention on the

14 second sentence and the first bullet point:

15 "While there was no glaring evidence of effects on

16 mitochondrial function, we are going to send

17 selected samples for assay of very long chain

18 fatty acids to further investigate the possibility

19 that peroxisomes are affected."

20 Do you see that?

21 A. Yes.

22 Q. Do you recall a discussion about

23 undertaking analysis of long chain fatty acids in

24 connection with the six-week study?

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1 THE VIDEOGRAPHER: Going off the record.

2 Time now is 11:51 a.m.

3 (WHEREUPON, discussion was had

4 off the record.)

5 THE VIDEOGRAPHER: We're back on the record.

6 Time now 12:01 p.m.

7 MR. ZWICKER: I have no further questions

8 today.

9 MR. LORENZINI: I have a few questions.

10 EXAMINATION

11 BY MR. LORENZINI:

12 Q. Dr. Loberg, could you turn to Exhibit

13 8, please? Do you recall testifying earlier about

14 some toxicology studies that according to the

15 documents were put on hold at some point in time?

16 A. Yes.

17 Q. I because want to go back over that to

18 clarify some of the timing issues. I think you

19 testified Exhibit 8 reflects a presentation that

20 you gave at the April 12, 2001 meeting; is that

21 correct?

22 A. Yes.

23 Q. Do you have any reason to believe that

24 these MMPI Working Group meeting minutes do not

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1 accurately reflect your presentation at that  
2 meeting?

3 A. I have no reason to believe so, no.

4 Q. I'll go ahead and read it for the  
5 record. Under the second bullet point, it states:  
6 "No steatosis was noted in either treated group.

7 There is no glaring evidence of effects on  
8 mitochondrial function, however, selected samples  
9 will be sent out for assay of very long chain  
10 fatty acids, VLCFA, to further investigate the  
11 possibility that peroxisomes are affected."

12 Based on this summary of your  
13 presentation at the April 12, 2001 meeting, what  
14 was the status of the analysis of very long chain  
15 fatty acids as of April 12, 2001?

16 MR. ZWICKER: Objection.

17 BY THE WITNESS:

18 A. Based on these minutes, the status of  
19 that assay that the samples were going to be that  
20 the samples were going to be sent out for assay.

21 BY MR. LORENZINI:

22 Q. According to these April 12, 2001  
23 minutes, as of April 12, 2001, was the analysis of  
24 the very long chain fatty acids on hold?

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1 A. No, not as of April 12.

2 Q. Could you turn to Exhibit 10, please.

3 For the record, this is the oncology status report

4 dated May 11, 2001. Could you turn to Page 2,

5 Section 4, Toxicology? And if you'll look at the

6 third sentence, it states: "While there is no

7 glaring evidence of effects on mitochondrial

8 function, we are going to send selected samples

9 for assay of very long chain fatty acids to

10 further investigate the possibility that

11 peroxisomes are affected. Draft results are

12 currently available and the report is expected by

13 6, 2001."

14 Do you see that?

15 A. Yes.

16 Q. Do you have any reason to believe that

17 this oncology status report dated May 11, 2001

18 does not accurately reflect the status of

19 toxicology as of that date?

20 A. No, I have no reason to believe so.

21 Q. According to your reading of this

22 document, what was the status of Abbott's analysis

23 of very long chain fatty acids from the rat study

24 as of May 11, 2001?

Loberg, Lise (Linked) 02/02/2007 9:27:00 AM

1 MR. ZWICKER: Objection. Lacks foundation.

2 BY THE WITNESS:

3 A. From these minutes, it appears that the  
4 assay was still planned to continue.

5 BY MR. LORENZINI:

6 Q. According to this oncology status  
7 report, was the very long chain fatty acid  
8 analysis still on hold?

9 A. No, not according to this report.

10 Q. I believe you testified earlier that  
11 the toxicology section of these oncology status  
12 reports that the information there would have been  
13 provided either by you or Bill Bracken; is that  
14 correct?

15 A. Yes, I believe this would have come  
16 from meeting minutes.

17 Q. From which meeting minutes?

18 A. The previous Working Group meeting.

19 Q. So the MMPI Working Group meeting just  
20 prior to May 11, 2001?

21 A. Yes, correct.

22 Q. And so it would have come from your  
23 presentation at that meeting?

24 A. Yes, that's correct.

Loberg, Lise (Linked) 02/02/2007 9:27:00 AM

1 Q. And in your presentations to the MMPI  
2 Working Group, did you always try to be as  
3 accurate as possible concerning the status of  
4 toxicology?

5 A. Yes.

6 Q. Do you have any reason to believe that  
7 the analysis of very long chain fatty acids was on  
8 hold any time prior to or on May 11, 2001?

9 A. No, I have no reason to believe that  
10 that was on hold at that time.

11 Q. So if the analysis of very long chain  
12 fatty acids was at some point placed on hold, that  
13 would have been after May 11, 2001?

14 A. Correct.

15 MR. LORENZINI: I have no further questions.

16 MR. ZWICKER: I need a minute. Why don't we  
17 go off the record.

18 THE VIDEOGRAPHER: Going off the record.

19 Time now is 12:01 p.m.

20 (WHEREUPON, a recess was had.)

21 THE VIDEOGRAPHER: We're back on the record.

22 Time now is 12:09.

23 FURTHER EXAMINATION

24 BY MR. ZWICKER:

Loberg, Lise (Linked) 02/02/2007 9:27:00 AM

1 Q. Dr. Loberg, take a look at Exhibit

2 No. 10.

3 Q. Under Section IV, Toxicology, do you

4 see that?

5 A. Yes.

6 Q. It says: "While there is no glaring  
7 evidence of effects on mitochondrial function, we  
8 are going to send selected samples for assay of  
9 very long chain fatty acids to further investigate  
10 the possibility that peroxisomes are affected."

11 Do you see that?

12 A. Yes.

13 Q. Isn't it true what's contemplated there  
14 is the sending out of samples for analysis?

15 A. Yes.

16 Q. In fact, the actual analysis of those  
17 samples was not undertaken by Abbott; isn't that  
18 true?

19 MR. LORENZINI: Objection. Vague and  
20 ambiguous.

21 BY THE WITNESS:

22 A. Yes, if the samples were being sent  
23 out, then they are being analyzed at a laboratory  
24 outside of our laboratories in Abbott.

1 BY MR. ZWICKER:

2 Q. But there is a distinction between  
3 sending data out for analysis and actually  
4 analyzing it, isn't there?

5 MR. LORENZINI: Objection. Vague and  
6 ambiguous.

7 BY THE WITNESS:

8 A. In this case, it would be samples that  
9 were sent for measurement of the very long chain  
10 fatty acids.

11 BY MR. ZWICKER:

12 Q. Isn't true that as of June 6, no  
13 analysis of those long chain fatty acids had been  
14 undertaken?

15 MR. LORENZINI: Objection. Lacks foundation.

16 BY MR. ZWICKER:

17 Q. Take a look at Exhibit 14, Page 2,  
18 No. 2.

19 MR. LORENZINI: Can the Reporter please  
20 repeat the question.

21 (WHEREUPON, the record was  
22 read by the reporter.)

23 MR. LORENZINI: Objection. Lacks foundation,  
24 calls for speculation.

Loberg, Lise (Linked) 02/02/2007 9:27:00 AM

1 BY THE WITNESS:

2 A. That appears to be true from this

3 e-mail.

4 BY MR. ZWICKER:

5 Q. So based on the two documents you

6 looked at, the long chain fatty acids were sent

7 out for analysis but never analyzed, at least as

8 of June 7, right?

9 MR. LORENZINI: Objection. Lacks foundation.

10 Calls for speculation.

11 BY THE WITNESS:

12 A. I can't say for sure whether the

13 samples were sent out or not based on the

14 information that we have.

15 BY MR. ZWICKER:

16 Q. But you can say based on the

17 information we have that as of June 6, those

18 samples were never analyzed, right?

19 MR. LORENZINI: Objection. Lacks foundation.

20 BY THE WITNESS:

21 A. Correct.

22 MR. ZWICKER: Nothing further.

23 MR. LORENZINI: I have nothing further.

24 THE VIDEOGRAPHER: Going off the record. The

LISE LOBERG, FEBRUARY 2, 2007

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1                   UNITED STATES DISTRICT COURT  
2                   FOR THE  
3                   DISTRICT OF MASSACHUSETTS  
4 JOHN HANCOCK LIFE INSURANCE         )  
5 COMPANY, et al.,                      )  
6                   Plaintiffs,         ) Civil Action No.  
7                   -vs-                 ) 05-11150-DPW  
8 ABBOTT LABORATORIES,                 )  
9                   Defendant.         )

10                  I hereby certify that I have read the  
11 foregoing transcript of my deposition given at the  
12 time and place aforesaid, consisting of Pages 1 to  
13 109, inclusive, and I do again subscribe and make  
14 oath that the same is a true, correct and complete  
15 transcript of my deposition so given as aforesaid,  
16 and includes changes, if any, so made by me.

17

18                   LISE LOBERG

19

20 SUBSCRIBED AND SWORN TO  
21 before me this                   day  
22 of                               , A.D. 200 .

23

24                   Notary Public

## Errata Sheet

Page: 1 Of Total Pages: 2

I wish to make the following changes to my deposition/statement:

Page #: 48, Line #: 11As appears in Transcript: issuesTo: tissuesReason: typographical errorPage #: 58, Line #: 6As appears in Transcript: functionsTo: fractionsReason: incorrect wordPage #: 60, Line #: 24As appears in Transcript: issuesTo: tissuesReason: typographical errorPage #: 80, Line #: 5As appears in Transcript: phraseTo: phaseReason: typographical error11-Apr-2007  
DATE  
DEPONENT'S SIGNATURE

Errata Sheet

Page: 2 Of Total Pages: 2

I wish to make the following changes to my deposition/statement:

Page #: 87, Line #: 24

As appears in Transcript: Cheri

To: Sherry

Reason: misspelling

Page #:   , Line #:   

As appears in Transcript: \_\_\_\_\_

To: \_\_\_\_\_

Reason: \_\_\_\_\_

Page #:   , Line #:   

As appears in Transcript: \_\_\_\_\_

To: \_\_\_\_\_

Reason: \_\_\_\_\_

Page #:   , Line #:   

As appears in Transcript: \_\_\_\_\_

To: \_\_\_\_\_

Reason: \_\_\_\_\_

11-Apr-2007  
DATE

  
DEPONENT'S SIGNATURE

# **Deposition Exhibit 3**

**D's Exhibit LY**

**MMPI WORKING GROUP MEETING MINUTES**

1/11/01

**Objective: Overall Project Update****Toxicology Review***Lise Loberg*

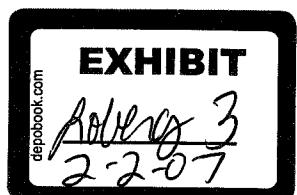
- There are currently two ongoing tox studies in rats, a six week study and a three month GLP study (with recovery). An overview of the study design and endpoints of interest was presented for the six week study (see attached slide – Tox Overheads 1&2). The main purpose of the six week study is to determine an etiology and mechanism for the steatosis noted in previous tox studies.
- Study timelines were presented for both studies (see attached slide – Tox Overhead 3). Draft results from the six week study should be available 5/01 and draft results with histopathology from the three month study should be available 7/01.
- The proposed three month tox study in monkeys is on hold until we receive feedback from the FDA at the pre-IND meeting.

**Chem Sciences***Steve Wittenberger*

- A review of the 2001 drug substance needs to re-supply the clinical studies was presented. There is currently enough product for the first two capsule campaigns in 2001, however, we will need to manufacture product for the third campaign.
- 10-15 kg of drug are anticipated from the first 2001 campaign (beginning in April, drug available in May). 6.5 kg are needed for the clinical studies (Phase I ex-US and Phase I US).
- The formulation/automation work for Phase II will be performed later this year; 1 kg of drug substance will be needed.
- A request for bulk drug was made to support the veterinary study proposed by Khanna (see Discovery section below). It was noted that non-GLP drug could be used for veterinary studies rather than using leftover bulk drug from the GLP runs.
- The go-ahead was given to begin purchasing starting materials to have on hand for future runs.
- Steve communicated their department's goal of removing bulk substance availability from the rate limiting path. A commitment was made to produce enough bulk substance to support the transition team activities (provided the activities are communicated with sufficient time to plan a synthetic campaign). Enough bulk substance will be produced and delivered 6/01 to re-supply the clinical study, start the "Phase II" formulation work and perform the Khanna study (20kg should be more than enough).

**Discovery***Steve Davidsen*

- The proposal submitted by Khanna for an open-label veterinary study with ABT-518 in naturally occurring tumors was presented (see attached slide – Khanna proposal). Due to the large amount of bulk drug needed for the proposed study (9 kg), some potential abbreviated studies and study designs were discussed.
- Bob Hansen will follow-up with Khanna to discuss study design, drug needs, timelines, cost, and so on. In addition, Bob will talk to Khanna about coming in a presenting to the group.



**MMPI WORKING GROUP MEETING MINUTES**

1/11/01

**PARD***John Cannon*

- A review of the 2001 capsule campaigns was presented (see attached slide - PARD). Note: Assumes a final projected dose of 1000mg (i.e., worst case); lower doses will result in a significant reduction of bulk substance usage.
- Contract negotiations are in progress with MDS Pharma in Tampa for the first 200mg capsule run of 2001. We anticipate knowing by February what manufacturing method they will use in order to meet the 5/01 delivery timeline for the Phase I studies.
- The placement decision for the three subsequent 2001 campaigns is still in progress (either IDC or MDS). When all necessary information is available a proposal will be prepared for completion of these campaigns at MDS and/or IDC.

**Metabolism Review***Dean Hickman*

- The preliminary results of the competitive inhibition experiments conducted at CEDRA indicate that the metabolites (at 2 and 20  $\mu$ M) are not competitive inhibitors (< 50% inhibition) of any pharmaceutically important CYP enzyme in humans (see attached slide- Metab 2). Furthermore, ABT-518 appears to be an inhibitor of only CYP3A under these conditions.
- The preliminary results of the mechanism based inhibition of CYP3A by ABT-518 and metabolites have been received from CEDRA but are still under review.
- Technical difficulties associated with the determination of Ki and Kinact for ABT-518 and some reference compounds are being reviewed. Estimates for some of these parameters will not be available by the end of January as originally expected.
- The in-life portion of a small Rat ADME study with [14C] ABT-518 has been completed and samples are being analyzed currently.

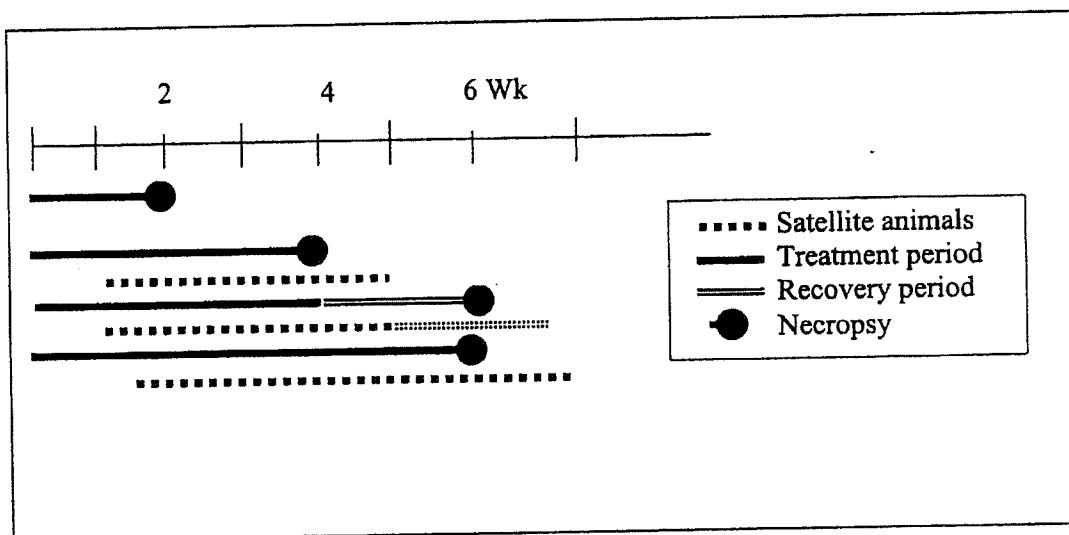
**Clinical Update***Diane D'Amico*

- A "best case scenario" timeline was presented for ABT-518 through Phase II (see attached slide - Clinical Timeline). All dates for the Phase I ex-US study were estimated using a four week EC approval time, however, EC approval may last as long as six weeks. The timelines for tox results were estimated and had not been confirmed by the tox team prior to the meeting (Note: See tox section for confirmed estimates). The IND timelines were taken directly from the Transition Strategy and will be discussed in detail during an internal IND meeting scheduled for 1/12/01.
- The first EC meeting was held on 1/9/01; initial feedback indicates minor changes and possible EC approval within two weeks.
- A teleconference will be scheduled to discuss the status of the PK method development and validation that is being performed by NKI's lab.

**Other***Steve Davidsen*

- Steve suggested that the group considers looking at a back-up to ABT-518 stating that most drug companies try at least three drugs per class in humans. Steve suggested the diol (one of the ABT-518 metabolites) since it has a shorter half-life, increased potency, metabolites that may or may not accumulate and we already have some data on it.

**Six-week Oral Hepatotoxicity Study of Abbott-291518 in Rats  
(TA00-231)**



**Six-week Oral Hepatotoxicity Study of Abbott-291518 in Rats  
(TA00-231)**

<b>Endpoint of interest</b>	<b>Tissue</b>
Clinical Chemistry ALT, AST, GGT Bile acids Free fatty acids Lactate/pyruvate	Blood
Urinalysis Ketones	Urine
Histopathology	Liver
Electron microscopy	Liver
Plasma drug levels	Blood
Mitochondrial membrane potential and mass	Freshly isolated hepatocytes
Mitochondrial respiration	Freshly isolated liver mitochondria
GSH/GSSG	Frozen liver mitochondria and/or frozen liver tissue
Fatty acid peroxidation in peroxisomes	Frozen liver tissue
<i>ATP/glycogen</i> <i>Lactate/pyruvate</i> <i>Lipid peroxidation</i> <i>Cytochrome C oxidase activity</i> <i>Enzymes/cofactors specific for fatty acid oxidation or oxidative phosphorylation</i> <i>Expression of mitochondrial genes encoding electron transport chain enzymes</i>	<i>Frozen liver tissue</i>

**Toxicity Studies of Abbott-291518**  
**Proposed Data Availability**

	Jan	Feb	Mar	Apr	May	Jun	Jul
Histo, Clin Chem, Urinalysis	X	X	X				
Mitochondrial assays - fresh		X	X				
Mitochondrial assays - frozen			X		?	?	
Plasma drug levels				?	?	?	
Electron microscopy				?	?	?	
Report due: Jun 2001				X	X	X	X

**6-Wk study (TA00-231)**

Histo, Clin Chem, Urinalysis  
 Mitochondrial assays - fresh  
 Mitochondrial assays - frozen  
 Plasma drug levels  
 Electron microscopy  
 Report due: Jun 2001

**3-Mo study (TA00-230)**

Hemat, Clin Chem, Urinalysis  
 Histopathology (liver)  
 Histopathology (full)  
 Plasma drug levels  
 Electron microscopy  
 Report due: Sept 2001

**Effect of ABT-518 in Naturally Occurring Tumors**  
**Open Label Veterinary Trial – Chand Khanna, NIH**

❖ Full Study: (analogous to ABT-526)

- open label study of single agent ABT-518 versus measurable (histologically confirmed) cancers in dogs and cats
  - dogs (50 cases/year; up to 6 months); ca. 7.3 kg
  - cats (35 cases/year; up to six months); ca. 1.5 kg

❖ Possible Abbreviated Studies :

- dogs with failing lymphoma (ca. 20 cases/year)
- cats with oral squamous cell carcinoma
- dogs failing ABT-526 therapy

# **Deposition Exhibit 8**

**D's Exhibit MH**

**MMPI WORKING GROUP MEETING MINUTES****4/12/01****Objective: Overall Project Update****Toxicology***Lise Loberg*

- An update of the two current toxicology studies was presented (see attached slides – MMPI Toxicology Update).
- The in-life phase of the six-week study has been completed. The study was designed to answer two questions: 1) Does steatosis occur in all treatment groups (low, mid and high dose) and 2) Will steatosis occur with continued dosing versus only in recovery. Results were similar to the four-week study (hepatocellular steatosis in the higher dose recovery group). No steatosis was noted in either treated group. There is no glaring evidence of effects on mitochondrial function, however, selected samples will be sent out for assay of very long-chain fatty acids (VLCFA) to further investigate the possibility that peroxisomes are affected. The study did not provide an etiology for the steatosis, but one possible explanation may be that the steatosis is an effect of re-feeding.
- Necropy analysis of samples from the 3-month study was put on hold until further notice.

**PARD***John Cannon*

- A clinical supplies update was presented (see attached slides – MMPI Drug Update).
- The first 200 mg capsule campaign (4,140 capsules) was delivered to IDS for the clinical supply.
- PARD is still investigating the lower than expected yield rate of 75% versus the expected 95%. To date, it is suspected that the bulk density of sieved drug and standard deviation of empty capsules account for the yield difference.

**Process Research and Development in GPRD***Steve Wittenberger*

- Review of the planned timelines for bulk drug manufacturing was presented (see attached slides – MMPI Bulk Plan).
- Bulk drug production was put on hold until further notice. Bulk drug needs and timelines must be re-evaluated.

**Metabolism***Dean Hickman*

- An overview of the ongoing metabolism work was presented (see attached slides – MMPI Metabolism Update).
- Results from a single dose administration using intact male rats (N=2) showed drug metabolites are eliminated primarily through feces. Results from a single dose administration using bile duct cannulated rats (N=2) showed drug metabolites are eliminated primarily through bile. The profile of metabolites was very different in the bile duct cannulated rats.
- A new metabolite, sulphonic acid, has been identified in rats. It was not seen in the earlier toxicology studies for one of two reasons: it elutes very early (in the void) on the HPLC system or it co-eluted with another analyte.



**MMPI WORKING GROUP MEETING MINUTES**

**4/12/01**

- Re-analysis of rat and monkey tissue and plasma samples for sulphonic acid after multiple dosing will take place. Analysis of human plasma for sulphonic acid after multiple dosing of ABT-518 should be considered (investigative, non-GLP pilot study?)

**Clinical**

*Diane D'Amico*

- Two patients have enrolled in study M00-235. One patient prematurely discontinued and the other patient is currently active. The active patient will have their Day 22 visit next week. Two more patients are scheduled to dose on 4/23/01.
- The third and final PK method validation run was completed in the Netherlands (NKI). NKI expects to assay the first human samples in May. All samples for each day of a single cohort will be assayed together.

# **Deposition Exhibit 9**

**D's Exhibit MI**

*Loberg 9*  
2-2-07

**MMPI MONTHLY MEETING AGENDA**  
4/12/2001, 10:30-12:00, AP6A-1A  
Objectives: To Review MMPI Project Status

Anne Hagey - Rotarians MD

I. Toxicology - L. Loberg

- Results from 6 week rat study
- 3 month rat - (RX phase ends this week)

II. PK - B. Carr/ M. Rieser

- No update

III. PARD - J. Cannon/ T. Garavalia/ S. Wittenberger

- Capsules analysis, Feton run- 101% against claim
- Process research is making additional drug

IV. Discovery - S. Davidson

- No Update

V. Metabolism - D. Hickman

- Rat ADME study update

↳ Single Dose

VI. Clinical- D. D'Amico

- PK method validation update- Netherlands
  - Day 1 PK samples from 2 patients collected
  - 2 patients enrolled, 1 active
  - 2 patients scheduled to enroll 4/23
  - IND document collection continues

**Next Team Venture Meeting**

When: Thursday, May 10, 2001

Where: AP6A-1A

Time: 10:30 - 12:00

\* Per D'Amico: Kill scenario : Weiden wants to make Go/No Go decision based on Competitor Data (C) ASCO ; committed.

IND Study: NIH : Nov/Dec-ish earliest start

I.

Will proceed  
w/ processing  
3 month sample  
until run  
here from  
10/97  
ceresoft

Findings: bile acids ↑ slight in HD ; GOT, bilirubin, & triglycerides similar to fatty acids HD  
① determine if steatosis occurs in young and old groups  
② if steatosis would occur w/ continued feeding (not just high) and ③ if steatosis would occur w/ continued feeding → No recovery only during  
majority of findings = high dose group = steatosis all dehydration, emaciation = high

Amt bile recovery : fresh isolates only  
No effects on mitochondrial function seen or on peroxisomal function (but only 1 alone)

stable cell-AT in both 4 & 6 wk groups

(in HD animals, not in recovery)

2<sup>nd</sup> isolation of cells not

mitochondrial AT

Not worth pursuing 2<sup>nd</sup> interpretation see

VLCFA very long Chain Fatty Acids

Why? ↓ weight & food consumption - HD animals only  
to determine effects on peroxisomes, hepatocyte, & metabolic stability  
not an uncommon finding  
VLCFA study does not correct anything new  
or explanation for steatosis when (lipidosis)

"F/u phenomenon" of steatosis

seen w/ acute pancreatitis

2<sup>nd</sup> cell proliferation ? liver tests w/? recovering of metabolism  
stop drug. Start eating again  
Can handle it.

Next time: in life 3 mo. clinical observations

III. Still investigation low yield

↳ bulk density of stored drug

more it packs more you take

→ bulk density ↑ (more compact) over time

and ② higher standard deviation of empty capsules : min narrow range for full capsules

↓ John: Preparing to make more material

3 steps, ready in June/J

each run will take 2 wks

expect 15 kg

+ needs to find out pilot plant

availability

Steve - Put on Hold Now; Will get back to you

Dickie - Late @ financial cuts (will we have?)

NH, Kharne studies need to be considered

II - Route of elimination - feces almost entirely

- profile of metabolites very different in bile duct cannulated animals & mice

slide - 1/2 life of 2 days for metabolite (picked up where parent left off). we pt taken out in next Pill

sulphonic acid → see a in rat tissue extracts now - wasn't seen before  
 - presume it's sulfonic acid (metabolite that has long  $\frac{1}{2}$  life)  
 - why didn't we see sulfonic acid?  
 We didn't see it in monkeys, etc. → only seeing this in rats so far  
 is started up new HPLC system to re-analyse rat & monkey  
 tissue & plasma samples

In Plasma: 518  $\mu$ g sulphonic acid

In Feces - see others

Should I change the protocol to have a w/o for sintron  
 & anti-coagulants

### Post Meeting

Strategy: Perry's Plan to Kill if Leader Says ~~No Go~~ No Go

Jeff wants to kill this; ARCO results neutral - negative; No  $\oplus$

Shelf ↓  
 Opt 0 KILL - Hard kill  
 Opt 1 Stop everything - try to out-innovate (sell); keep doing stability, etc; pt cohorts continue  
 Opt 2 Put it on pause until ???  
 Opt 3 Offer pre-emptive plan for development → show how it shows/doesn't show benefit  
 More forward (large claim)

Put a plan in place - knowing where they are & what will do

Auguron - Add on to therapy  
 Proximal disease vs advanced disease  
 ? joint effects?  
 (1) explore non-oncologic indications  
 (2) how do we study proximal vs advanced

If we cut Ph I now - w/o nothing finished - partner will partner up

SAFETY  
 ↓ joint - should answer in Ph II  
 ↓ prohibits chronic drug administration

Perry wants to give Jeff a white sheet now

Activity  
 PD → Interact tumor tissue in melanoma & head & neck  
 Xylography - approach

May even work by itself

↓  
 Locally invasive disease  
 (ACI), (BE), PIN, DCIS, early bladder, ...  
IIa - consistency measured  
 Can we relate/rx these?

Page ②

Other possibilities

Non Cancer:

MS  
fibrosis — hepatic fibrosis  
prolif ~~not~~ AA  
retinopathy

IPF =  
easy to measure  
very attractive  
field  
↓  
"immunology  
franchise"

Present Plan to John/Jeff now (or May 4, 5<sup>th</sup>)

Nobody has ever gotten approval  
for locally invasive disease.

History weak

Mirinistat works in MS models. Does ours? Not known.  
Can we do some pre-clinical work?

Steve: will give list of non-cancer to Loeffel & Perry to  
build stories for both

Finish Safety Study: \$X Spend  
If we move onto after — Gain \$X  
Show Benefit

"Enthusiasm is inversely proportional to knowledge" - Perry

# **Deposition Exhibit 10**

**D's Exhibit LZ**

# Oncology Status Report

**As Of: May 11, 2001**

## **ABT-518 (MMPI)**

### **M00-235 MD Study in Patients**

- **Meetings:**

- MMPI Team Meeting – 5/10/01 (Cancelled)
- MMPI Team Meeting – 6/7/01

- **Activities:**

1. **Clinical**

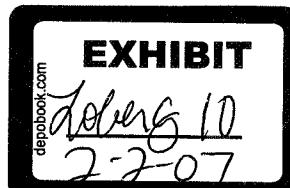
- During ASCO, Todd will meet with Schellen, Zonnenberg and Looman to discuss the progression of cohorts. The first cohort will complete Day 29 on 5/21/01; cohort #2 (50mg) will begin enrolling on 5/21/01 if a Go decision is granted.
- Preliminary feedback from the PK audit was good; no major observations noted. As soon as Matt provides the Dutch with feedback from the draft PK validation method report, the Dutch will prepare the final report for Abbott approval. Then, the Dutch will send Abbott a study plan for review and sign-off. After these two documents are final, the Dutch will be able to run patient samples (May).
- PD Validation: According to Prof. Voest, they have encountered high variability in measuring levels of MMP-2 and MMP-9 in both urine and blood. They now feel that pursuing bioactivity assays may be the best way to go. They are performing additional tests and will give us an answer next week.

2. **IND – No change from the previous version per D. D'Amico 5/11/01**

- We will continue to meet with the groups over the next few weeks to determine timelines for reports that will be included as part of the IND package.
- The Investigator's Brochure (IB) update will take place in June/July to include as much Toxicology data as possible. The clinical section, as well as any other sections, will also be updated. This new timeline will fit well with the timeline of out-licensing the compound this fall.

3. **Metabolism – No change from the previous version per D. Hickman 5/11/01**

- A major rat plasma metabolite has been tentatively identified by LC/MS/MS (we have not seen the reports from structural chemistry yet). Its structure, yet to be confirmed by NMR, is consistent with a biarylether sulphonic acid metabolite. A preliminary review of the literature (Medline, ISIS drug metabolism database and several drug metabolism texts) indicates that this is quite novel for a sulphone drug. This metabolite represents a new finding and given its prominence compared to



ABT-518 (sulfonic acid: ABT-518 AUC ratio of approximately 10 after a single dose) it will be something that we will want to look for in human plasma. We also plan to re-examine plasma/tissue extracts from preclinical tox studies (rat and monkey - ongoing) for this metabolite using radiolabeled isolate as a reference.

- CEDRA have reported their data on metabolism-based inhibition CYP3A in human liver microsomes. A draft report of ALL data was received on 12APR01. A preliminary look at the report suggests that of the 6 metabolites and ABT-518, only ABT-518 exhibits metabolism-based irreversible inhibition of CYP3A. The report appears to need a lot of work.

#### 4. Toxicology

- The 6-week rat study has been completed. Results were similar to the four-week study (hepatocellular steatosis in the recovery group, but not in the 4-week or 6-week treated groups). While there is no glaring evidence of effects on mitochondrial function, we are going to send selected samples for assay of very long-chain fatty acids (to further investigate the possibility that peroxisomes are affected). Draft results are currently available and the report is expected by 6/2001.
- The 3-month GLP rat study (both the in-life phase and recovery) has been completed. Processing of histopathology slides has been put on hold until further notice. Therefore, draft results without histopathology will be available by 7/2001. The histopathology results and report will follow.

#### 5. Drug Analysis

- The reanalysis of the monkey lab work is complete. The tabulation report is currently being written. The reanalysis of the rat is still underway.
- The 6-week and 3-month rat study samples have not yet been analyzed.

#### 6. Drug

- The NPRO packet for the ABT-518 capsules (200 mg) manufactures by MDS Pharma is in the final review by IDQA; approval of the lot is expected soon.

#### 7. Issues

- Review and confirm bulk drug manufacturing needs for IND studies (Bronson/D'Amico).

## Timeline

ABT-518  
Study  
M00-235

■ First Cohort  
Enrollment  
Complete: 4/23/01

■ First Patient  
Enrolled (25mg)  
3/12/01

■ Drug shipped to  
sites: 2/28/01 and  
3/1/01

■ Study Initiated  
14,15 Feb 2001

# **Deposition Exhibit14**

**D's Exhibit AW**



Lise I  
Loberg/LAKE/PPRD/ABBOTT  
06/06/2001 06:29 PM

To William M Bracken/LAKE/PPRD/ABBOTT@ABBOTT, Bruce A Trela/LAKE/PPRD/ABBOTT@ABBOTT, Ken R Majors/LAKE/PPRD/ABBOTT@ABBOTT, Chudy I Nduaka/LAKE/PPRD/ABBOTT@ABBOTT  
cc  
bcc  
Subject ABT-518 update

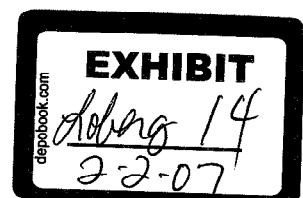
As you heard in this morning's meeting, ABT-518 is on indefinite hold. (I guess that's what you'd call it.) At tomorrow's MMPI Team Meeting, I will give an update on ongoing projects and timelines for concluding the project. Please take a look at the attached file and fill in any dates that you can. Thank you!

(Oh yeah, the meeting is at 10:30 and I'd like to stop over at the Technology Exchange before the meeting. I'd appreciate your update by 9am if possible. Sorry for the short notice.)



MMPI Toxicology Activities.doc

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### MMPI Toxicology Activities

#### Ongoing projects:

All studies completed (in-life) with reports in progress

1. Three-month rat toxicity study (TA00-230)  
In-life: complete  
Processing histopathology slides on hold  
Draft report (w/o histo, PK) completed \_\_\_\_\_  
Final report \_\_\_\_\_
2. Six-week rat hepatotoxicity study (TA00-231, non-GLP)  
Analysis of VLCFA on hold  
Draft report in progress; completed (w/o PK, VLCFA) 6/30/01
3. Four-week oral toxicity study in monkeys (TC00-072)  
Draft report (w/o PK) finished  
Final report \_\_\_\_\_
4. One-month oral toxicity study in rats (TA00-070)  
Draft report (w/o PK) finished  
Final report \_\_\_\_\_
5. Genotoxicity studies (TX00-132, TX00-133, TD00-134)  
Awaiting final reports from Covance  
TD00-134 awaiting PK

#### Completed projects:

6. Acute toxicity studies (TA00-100, TD00-101, TA00-102, TD00-103)  
All final reports issued

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